GRANTS, INNOVATION AND PRODUCT DEVELOPMENT

HIV PROJECT PORTFOLIO

2018

saMRC advancinglife

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SOUTH AFRICAN MEDICAL RESEARCH COUNCIL FUNDED PROJECTS:

THE **GRANTS, INNOVATION AND PRODUCT DEVELOPMENT (GIPD) DIVISION** OF THE **SAMRC** IS CURRENTLY FUNDING THE FOLLOWING **HIV/AIDS PROJECTS:**

HIV DIAGNOSTICS

1. A GIFT (GENITAL INFLAMMATION TEST) FOR HIV PREVENTION

PI: Lindi Masson (University of Cape Town)
Co PI: Jo-Ann Passmore (University of Cape Town)
Overall Aim: The project aims to develop a POC test device for genital inflammation as an indication of sexually transmitted infections or bacterial vaginosis, more specifically to identify women who have asymptomatic infections. The test will use a combination of validated cytokine biomarkers in a rapid test format. The aim of the test is to identify and treat STI cases that would generally be missed through syndromic management and thereby reduce the prevalence of STIs and BV and hence the associated HIV infection risk in South African women.

2. INCREASING THE CAPACITY OF AN HIV DRUG RESISTANCE TESTING PIPELINE TO FACILITATE THE IMPLEMENTATION OF HIGH-THROUGHPUT, COST-EFFECTIVE HIV RESISTANCE GENOTYPING IN SOUTH AFRICA AND OTHER RESOURCE-LIMITED SETTINGS

PI: Simon Travers (University of the Western Cape)
Overall Aim: The project aims to facilitate the scale up of an easy-to-use and cost-effective high through-put tool for the processing and analysis of Next Generation Sequencing (NGS) HIV drug resistance test sequence data. This includes development of a fully scalable, cloud based and flexible tool that will have no limits in relation to the number of analyses that can be run concurrently and that enables clinicians and researchers to easily analyse NGS data for the purposes of HIV-DRT without the need for a specialised bioinformatics expert. It will enable high-throughput, low-cost HIV drug resistance testing in South Africa and worldwide.

3. HIVSmart! TRANSITION TO SCALE

PI: Keertan Dheda (University of Cape Town)

Overall Aim: This project aims to develop and implement a transition to scale plan for an HIV self-testing and counselling strategy in southern Africa. It is a matched-control cohort study (quasi randomised impact evaluation design), aimed at demonstrating the impact of HIVSmart!, a self-testing strategy that combines an HIV self-test with an App, on access to and uptake of testing, detection of new infections, and linkages and retention in care. The project will also document patient-centred preferences for linkages to care. This project is a collaboration with McGill University.

HIV THERAPEUTICS

1. DEVELOPMENT OF A BETTER AND MORE ROBUST SECOND-LINE ANTIRETROVIRAL REGIMEN FOR HIV INFECTION

PI: Francois Venter (University of the Witwatersrand)

Overall Aim: This project aims to test a new, simpler, safer, more potent and potentially more cost-effective second line antiretroviral therapy for South Africa. It uses a randomised, open label switch study to assess the non-inferiority of low dose darunavir/ritonavir when compared with lopinavir/ritonavir, in combination with a nucleoside backbone, as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels after week 48. The secondary objective will be to assess the tolerability and safety of darunavir/ritonavir when switching to lopinavir/ritonavir, over these 48 weeks.

HIV VACCINES

1. NOVEL HIV VACCINE CANDIDATES FOR SOUTH AFRICA

PI: Anna-Lise Williamson (University of Cape Town)

Co-PIs: Ed Rybicki, Ros Chapman, Gerald Chege, and Nicola Douglass (University of Cape Town); Lynn Morris (National Institute for Communicable Diseases)

Overall Aim: The aim of the project is to develop novel HIV envelope antigens for higher yield and enhanced immunogenicity. Subtype C Envs will be produced as chimaeric molecules incorporating various fusions that promote stability, trimerisation and "protein body" particle formation. The antigens will be tested for immunogenicity in a variety of expression vectors, and as subunit proteins, in heterologous prime-boost protocols. The aim is to achieve higher yield and more immunogenic protein than production of conventional HIV gp160 or gp120.

2. VACCINE-MEDIATED EFFECTS ON IMMUNOLOGICAL, VIRAL AND CLINICAL FACTORS IN HIV BREAKTHROUGH INFECTIONS

PI: Carolyn Williamson (University of Cape Town)

Co-PIs: Lynn Morris (National Institute for Communicable Diseases); Fatima Laher (University of the Witwatersrand)

Overall Aim: Through the evaluation of breakthrough infections from vaccine trials in South Africa this project will identify vaccine-mediated effects on neutralising responses, viral sequences and subsequent disease progression. New approaches to identifying vaccine pressure will be developed and applied to determine whether signatures associated with MrkAd5 vaccine pressure in the Phambili trial impacted on viral replicative fitness and subsequent disease progression. In breakthrough infections from the SAAVI and HVTN204 Phase I/II trials, the project will evaluate the effect of Envelope vaccines on subsequent neutralising and non-neutralising antibody responses to natural infection.

3. BROADLY NEUTRALISING HIV ANTIBODIES, ADJUVANTS AND IMMUNOGENS

PI: Penny Moore (National Institute for Communicable Diseases)

Co-PIs: Lynn Morris (National Institute for Communicable Diseases); Carolyn Williamson (University of Cape Town); Wendy Burgers (University of Cape Town); Nigel Garrett (Centre for the AIDS Programme of Research - CAPRISA)

Overall Aim: This project aims to design and test novel cocktail HIV vaccines to elicit BCN antibodies based on lessons learned from natural infection. To do this, the project will i) map and isolate BCN mAbs from infected individuals, ii) evaluate viral evolution in natural infection to elucidate the viral variants responsible for eliciting BCN responses, iii) define host and microbiome factors conducive to the development of neutralisation breadth, and iv) recapitulate these processes in a non-human primate model through vaccination.

4. ISOLATION AND CHARACTERISATION OF MONOCLONAL ANTIBODIES FROM HIV-1 SUBTYPE C INFECTED INDIVIDUALS

PI: Lynn Morris (National Institute for Communicable Diseases)

Co-PIs: Jayanta Bhattacharya (Translational Health Science & Technology Institute [THSTI], India)

Overall Aim: The project builds on a successful collaboration between principal investigators from South Africa and India and aims to design and generate soluble trimeric HIV protein antigens for epitope mapping and B cell sorting, to isolate mAbs from selected patients in India and South Africa by antigen-specific B cell sorting and/or memory B cell culture, and to characterise the epitopes of mAbs that show the greatest breadth and potency.

5. PROOF OF CONCEPT STUDY FOR THE PRODUCTION AND CHARACTERISATION OF CAP256 MONOCLONAL ANTIBODIES IN PLANTS

PI: Rachel Chikwamba (Council for Scientific and Industrial Research)

Overall Aim: This proof of concept study aims to use low cost, plant based expression technologies to produce two locally identified monoclonal antibodies and test them for structural integrity and functionality. If successful, this represents an alternative platform for the production of mAbs suitable for human therapeutics in high yield and in a short period of time.

6. A NOVEL DUAL ANIMAL PRE-CLINICAL PLATFORM: ACCELERATING HIV VACCINE PRODUCT DEVELOPMENT IN SOUTH AFRICA

PI: Gerald Chege (University of Cape Town)
Co-PI: Muazzam Jacobs (University of Cape Town)
Overall Aim: The aim of this project is to establish a novel dual animal model preclinical platform consisting of a humanised mouse model for initial rapid screening of HIV vaccine candidates and a SHIV/Chinese rhesus macaque challenge model for subsequent assessment of the protective potential of promising Envelope- and vector-based candidates. Its successful establishment and validation will accelerate HIV vaccine product development and enhance capacity to conduct state-of-the-art translational medical research, including preclinical HIV research, in South Africa.

HIV PREVENTION

1. THE SELECTIVE DELIVERY OF BROAD-SPECTRUM METAL-BASED MICROBICIDES USING ALGINATE-ENCAPSULATION

PI: Leonard Damelin (National Institute for Communicable Diseases)
Co-PI: Caroline Tiemessen (National Institute for Communicable Diseases)
Overall Aim: This project builds on preliminary results using silver complexes encapsulated in alginate microbeads as a novel device for the delivery and selective release of silver-microbicides within the vaginal milieu during sexual intercourse/after ejaculation for the inactivation of both HIV and STIs. The project is aimed at identifying further silver and other metal complexes with increased microbicidal activity and/or increased delivery system compatibility, optimising alginate bead composition and size for optimal microbicide delivery and expanding testing to assess activity on other STIs, potential additive effects when used in combination with tenofovir and the effect on vaginal microflora and semen.

2. IMMEDIATE OR DEFERRED PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION: SAFE OPTIONS FOR PREGNANT AND LACTATING WOMEN - AN OPEN-LABEL RANDOMISED CONTROL STUDY

PI: Dhayendre Moodley (University of KwaZulu-Natal)
Overall Aim: This open-label randomised control study is designed to explore the safety of Truvada, in combination with current recommendations for prevention of sexually transmitted infections and HIV, when used as PrEP in HIV uninfected women at substantial risk during pregnancy and

lactation. It will compare the frequency and seriousness of adverse events in women receiving tenofovir/emtricitabine in pregnancy as opposed to women not receiving tenofovir/emtricitabine in pregnancy.

OTHER

1. THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES (ECHO) STUDY

PI: Helen Rees (Wits Reproductive Health and HIV Institute)

Overall Aim: Wits RHI is one of the four leading institutes running the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study, a multi-center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel Implant and Copper Intrauterine Devices (IUDs). The MRC is contributing towards the training and technical support to sites on community engagement aimed at creating an enabling environment in support of ECHO's recruitment and retention strategies.

2. THE WOMEN'S HEALTH, INJECTABLE CONTRACEPTION AND HIV STUDY (PART 1): RANDOMISED COMPARISON OF IMMUNOLOGICAL, HORMONAL, PHYSIOLOGICAL, PSYCHOLOGICAL AND BEHAVIOURAL EFFECTS OF NET-EN VERSUS DMPA CONTRACEPTION

PI: Mandisa Singata (Universities of Witwatersrand/Fort Hare and Eastern Cape Department of Health)

Co-PIs: J Smit (University of the Witwatersrand); Janet Hapgood (University of Cape Town)

Overall Aim: The aim of the study is to compare biological, immunological, hormonal, physiological, psychological and behavioural effects of alternative injectable progestogen contraceptives (NET-EN and DMPA IM) of relevance to adherence and HIV acquisition risk, and to assess the feasibility of a larger trial comparing HIV acquisition risk. The initial scope will include limited sentinel biological markers which will inform the need for further biological studies using archived specimens. Unlike previous observational studies, this will be a randomised trial, and will thus produce the most robust comparative data available to date on outcomes relevant to contraceptive counselling and HIV risk.

3. POPULATION BASED SURVEYS FOR HIV IN EASTERN CAPE ACCIDENT AND EMERGENCY DEPARTMENTS

PI: Andy Parrish (Walter Sisulu University)
Co-PIs: Tom Quinn (NIAID/NIH), Bhakti Hansoti (Johns Hopkins University)
Overall Aim: The aim of the project is to examine the current status of the HIV epidemic in the Eastern Cape (including East London, Mthatha and Port Elizabeth) within the context of Emergency Departments (EDs), which may provide a high yield avenue for HIV testing and linkage to care. The study involves implementing Provider Initiated Counseling and Testing (PICT) in the ED coupled with a blinded identity unlinked survey on waste/discarded sera to quantify the burden of undiagnosed HIV infection in the population of patients that present for care in the ED that would be missed with a PICT strategy.

4. IMPLEMENTING THE ANNUAL ANTENATAL HIV SEROPREVALENCE SURVEY IN SOUTH AFRICA 2017

PI: Adrian Puren (National Institute for Communicable Diseases)
Overall Aim: The overall objective is to determine the antenatal HIV prevalence amongst both first time and follow-up antenatal attendees in South Africa. The 2017 survey aims to carry out linked anonymous testing (LUT)–based antenatal HIV surveillance (with returning of test results) to address the core objectives of the survey retained from previous surveys and additional survey questions added this year. The survey will estimate HIV prevalence trends at national and provincial levels and HIV distribution across districts. In addition, the 2017 survey will obtain additional information to estimate: HIV incidence, performance along the 90-90-90 Joint United Nations programme on HIV/AIDS (UNAIDS) indicators, syphilis service uptake, and performance (specificity and sensitivity) of routine rapid testing.

5. HIV-1 POSITIVE SOUTH AFRICAN ELITE AND LONG TERM CONTROLLERS: VIRAL AND HOST TARGETS FOR HIV FUNCTIONAL CURE STRATEGIES

PI: Caroline Tiemessen (National Institute for Communicable Diseases)

Co-PIs: Neil Martinson (University of the Witwatersrand); Marion Vermeulen (South African National Blood Services (SANBS)); Photini Kiepiela (MRC HIV Prevention Research Unit); Maria Papathanasopoulos (University of the Witwatersrand); Michele Ramsay (University of the Witwatersrand)

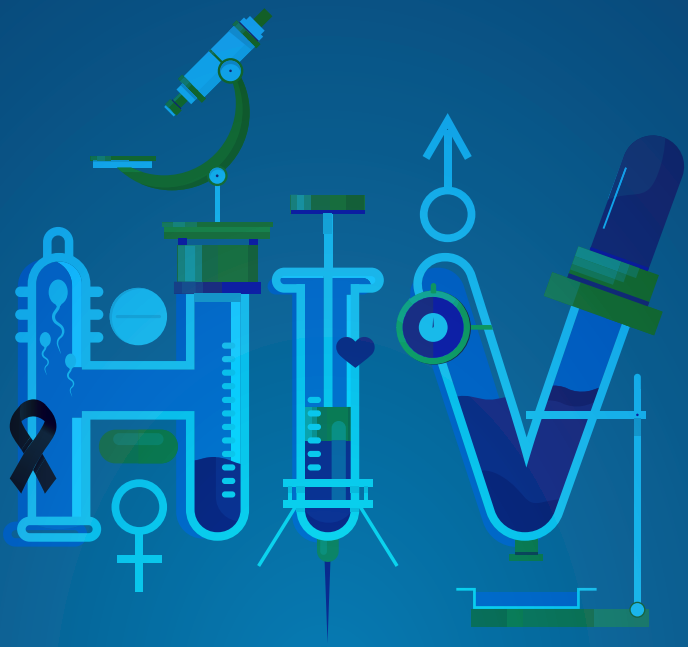
Overall Aim: The aim of this project is to establish a pipeline of key targets, both viral and host, which can be developed as future feasible therapeutic approaches for attaining a "functional cure" to HIV-1. This will be achieved through a comprehensive study of the human model that represents functional cure, i.e. elite controllers (ECs) and long term non-progressors (LTNPs), the identification of biosignatures that describe different phenotypes of HIV control, and the identification of individuals that harbour as yet undiscovered pathways of control.

6. CHARACTERISATION OF THE HIV RESERVOIR IN THE SOUTH AFRICAN CHILD WITH HIV REMISSION

PI: Caroline Tiemessen (National Institute for Communicable Diseases)

Co-PI/Collaborator: Avy Violari (Perinatal HIV Research Unit)

Overall Aim: The aim of this project is to gain insight into the viral characteristics associated with the state of HIV-1 remission in a South African child that has achieved sustained virological control for nine years post-ART interruption. The project will include a detailed analysis of HIV-1 provirus reservoir and establish the potential for replication-competence based on the presence of intact non-defective provirus (next generation sequencing), cell-associated multiply spliced (ms) RNA (TILDA) and translation-competence at the single cell level (RNA flow-FISH). The project is designed to provide an in-depth understanding of the virus genetic changes that have occurred over time of infection, potentially through host immune response pressure and ART pressure, and to establish to what extent genetically intact proviruses, potentially capable of producing virus, populate the reservoir.



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